ROBBINS Basic Pathology

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CHAPTER 13

Kidney and Its Collecting System

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The kidney is a structurally complex organ that has evolved to carry out a number of important functions: excretion of the waste products of metabolism, regulation of body water and salt, maintenance of acid balance, and secretion of a variety of hormones and prostaglandins. Diseases of the kidney are as complex as its structure, but their study is facilitated by dividing them into those that affect its four components: glomeruli, tubules, interstitium, and blood vessels. This traditional approach is useful because the early manifestations of diseases that affect each of these components tend to be distinctive. Furthermore, some structures seem to be more vulnerable to specific forms of renal injury; for example, glomerular diseases are often immunologically mediated, whereas tubular and interstitial disorders are more likely to be caused by toxic or infectious agents. However, some disorders affect more than one structure, and functional interdependence of structures in the kidney means that damage to one component almost always secondarily affects the others. Thus, severe glomerular damage impairs the flow through the peritubular vascular system; conversely, tubular destruction, by increasing intraglomerular pressure and inducing cytokines and chemokines, may induce glomerular sclerosis. Whatever the origin, there is a tendency for chronic renal disease ultimately to damage all four components of the kidney, culminating in *end-stage kidney disease*. For these reasons, the early signs and symptoms of renal disease are particularly important in discerning the initiating cause of the disease, and therefore are referred to in the discussion of individual diseases. The functional reserve of the kidney is large, and much damage may occur before renal dysfunction becomes evident.

CLINICAL MANIFESTATIONS OF RENAL DISEASES

The clinical manifestations of renal disease can be grouped into reasonably well-defined syndromes. Some are peculiar to glomerular diseases and others are shared by several renal disorders. Before we list the syndromes, a few terms must be defined.

Azotemia is an elevation of blood urea nitrogen and creatinine levels and usually reflects a decreased glomerular filtration rate (GFR). GFR may be decreased as a consequence of intrinsic renal disease or extrarenal causes. *Prerenal azotemia* is encountered when there is hypoperfusion of the kidneys, which decreases GFR *in the absence of parenchymal damage*. *Postrenal azotemia* results when urine flow is obstructed below the level of the kidney. Relief of the obstruction is followed by correction of the azotemia.

When azotemia gives rise to clinical manifestations and systemic biochemical abnormalities, it is termed *uremia*. Uremia is characterized not only by failure of renal excretory function but also by a host of metabolic and endocrine alterations incident to renal damage. There is, in addition, secondary gastrointestinal (e.g., uremic gastroenteritis); neuromuscular (e.g., peripheral neuropathy); and cardiovascular (e.g., uremic fibrinous pericarditis) involvement.

We now turn to a brief description of the major renal syndromes:

- *Nephritic syndrome* results from glomerular injury and is dominated by the acute onset of usually grossly visible hematuria (red blood cells and red cell casts in urine), proteinuria of mild to moderate degree, azotemia,

edema, and hypertension; it is the classic presentation of acute poststreptococcal glomerulonephritis.

- *Nephrotic syndrome* is a glomerular syndrome characterized by heavy proteinuria (excretion of greater than 3.5 g of protein/day in adults), hypoalbuminemia, severe edema, hyperlipidemia, and lipiduria (lipid in the urine).
- *Asymptomatic hematuria* or non-nephrotic *proteinuria*, or a combination of these two, is usually a manifestation of subtle or mild glomerular abnormalities.
- *Rapidly progressive glomerulonephritis* is associated with severe glomerular injury and results in loss of renal function in a few days or weeks. It is manifested by microscopic hematuria, dysmorphic red blood cells and red cell casts in the urine sediment, and mild to moderate proteinuria.
- *Acute kidney injury* is dominated by oliguria or anuria (no urine flow), and recent onset of azotemia. It can result from glomerular injury (such as rapidly progessive glomerulonephritis), interstitial injury, vascular injury (such as thrombotic microangiopathy), or acute tubular injury.
- *Chronic kidney disease*, characterized by prolonged symptoms and signs of uremia, is the result of progressive scarring in the kidney from any cause and may culminate in end-stage kidney disease, requiring dialysis or transplantation.
- *Urinary tract infection* is characterized by bacteriuria and pyuria (bacteria and leukocytes in the urine). The infection may be symptomatic or asymptomatic, and it may affect the kidney (*pyelonephritis*) or the bladder (*cystitis*) only.
- *Nephrolithiasis* (renal stones) is manifested by renal colic, hematuria (without red cell casts), and recurrent stone formation.

In addition to these renal syndromes, *urinary tract obstruction* and *renal tumors* also commonly present with signs and symptoms related to renal dysfunction and are discussed later.

GLOMERULAR DISEASES

Disorders affecting the glomerulus encompass a clinically important category of renal disease. The glomerulus consists of an anastomosing network of capillaries invested by two layers of epithelium. The visceral epithelium (composed of podocytes) is an intrinsic part of the capillary wall, whereas the parietal epithelium lines Bowman space (urinary space), the cavity in which plasma ultrafiltrate first collects. The glomerular capillary wall is the filtration unit and consists of the following structures (Figs. 13–1 and 13–2):

- A thin layer of fenestrated *endothelial cells*, each fenestra being 70 to 100 nm in diameter.
- A *glomerular basement membrane* (GBM) with a thick, electron-dense central layer, the *lamina densa*, and thinner, electron-lucent peripheral layers, the *lamina rara interna* and *lamina rara externa*. The GBM consists of collagen (mostly type IV), laminin, polyanionic proteoglycans, fibronectin, and several other glycoproteins.
- *Podocytes*, which are structurally complex cells that possess interdigitating processes embedded in and adherent to the lamina rara externa of the basement membrane. Adjacent *foot processes* are separated by 20- to 30-nm-wide *filtration slits*, which are bridged by a thin slit diaphragm composed in large part of nephrin (see further on).
- The glomerular tuft is supported by *mesangial cells* lying between the capillaries. Basement membrane–like mesangial matrix forms a meshwork through which the mesangial cells are scattered. These cells, of mesenchymal origin, are contractile and are capable of proliferation, of laying down collagen and other matrix components, and of secreting a number of biologically active mediators.

Normally, the glomerular filtration system is extraordinarily permeable to water and small solutes and almost completely impermeable to molecules of the size and molecular charge of albumin (a 70,000-kDa protein). This selective permeability, called glomerular barrier function, discriminates among protein molecules according to their size (the larger, the less permeable), their charge (the more cationic, the more permeable), and their configuration. The characteristics of the normal barrier depend on the complex structure of the capillary wall, the integrity of the GBM, and the many anionic molecules present within the wall, including the acidic proteoglycans of the GBM and the sialoglycoproteins of epithelial and endothelial cell coats. *The podocyte is also crucial to the maintenance of glomerular barrier function*. Podocyte slit diaphragms are important diffusion barriers for plasma proteins, and podocytes are also largely responsible for synthesis of GBM components.

In the past few years, much has been learned about the molecular architecture of the glomerular filtration barrier. *Nephrin*, a transmembrane glycoprotein, is the major component of the slit diaphragms between adjacent foot processes. Nephrin molecules from adjacent foot processes bind to each other through disulfide bridges at the center of the slit diaphragm. The intracellular part of nephrin interacts with several cytoskeletal and signaling proteins (Fig. 13–1). Nephrin and its associated proteins, including *podocin*, have a crucial role in maintaining the selective permeability of the glomerular filtration barrier. This role is dramatically illustrated by rare hereditary diseases in which mutations of nephrin or its partner proteins are associated with abnormal leakage into the urine of plasma proteins, giving rise to the nephrotic syndrome (discussed later). This observation suggests that acquired defects in the function or structure of slit diaphragms constitute an important mechanism of proteinuria, the hallmark of the nephrotic syndrome.

Glomeruli may be injured by diverse mechanisms and in the course of a number of systemic diseases (Table 13–1). Immunologically mediated diseases such as systemic lupus erythematosus, vascular disorders such as hypertension and hemolytic uremic syndrome, metabolic diseases such as diabetes mellitus, and some purely hereditary conditions such as Alport syndrome often affect the glomerulus. These are termed *secondary glomerular diseases* to differentiate them from those in which the kidney is the only or predominant organ involved. The latter constitute